

**Copy of Original IDS
Filed July 13, 1998**

Please date-stamp this self-addressed stamped postcard indicating the date that the PTO received the following documents:

Applicant: Behn B Chalmers Examiner:

Serial No.: 091060,188 Art Unit:

Filing Date: Apr. 14, 1998

Title: A method of Identifying Modulators of Cell Surface

Documents: Membrane Receptors Label in the Treatment of Disease

1. Completed modified PTO form 1449A 3 1449B
2. Copies of references listed on 1449A 3 1449B
3. duplicate of form 1449A 3 1449B
4. Cover letter



In re Application of: Dominic P. BEHAN and Derek T. CHALMERS
Serial No: 09/060,188
Filed: April 14, 1998
For: *A Method of Identifying Modulators of Cell Surface Membrane
Receptors Useful in the Treatment of Disease*

July 8, 1998

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

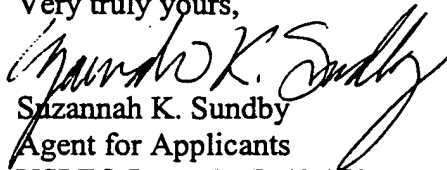
Transmitted herewith for filing is an Invention Disclosure Statement for the continuation-in-part patent application of Dominic P. Behan and Derek T. Chalmers entitled: *A Method of Identifying Modulators of Cell Surface Membrane Receptors Useful in the Treatment of Disease* filed April 14, 1998 and assigned to Arena Pharmaceuticals, Inc.

This Invention Disclosure Statement is submitted before the mailing date of the first Office action on the merits under 37 CFR § 1.97(b)(3). The filing of this Invention Disclosure Statement shall not be construed as a representation that a search has been made, nor shall it be construed as an admission that the information cited in the statement is, or is considered to be, material to patentability as defined under § 1.56(b).

Enclosed please find the following documents relating this submission:

1. A completed modified form PTO 1449A and 1449B, consisting of 9 pages,
2. Copies of references listed in the modified form PTO 1449A and 1449B,
3. A duplicate of the completed modified form PTO 1449A and 1449B for return to Applicants;
and
4. A self-addressed stamped postcard.

Very truly yours,


Suzannah K. Sundby
Agent for Applicants
USPTO Reg. No. P-43,172

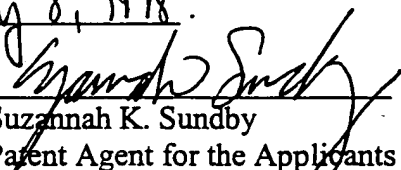
cc: Richard P. Burgoon, Jr.
Vice President & General Counsel
Arena Pharmaceuticals, Inc.
6166 Nancy Ridge Drive
San Diego, CA 92121

Enclosures

INFORMATION DISCLOSURE STATEMENT

In re Application of: Dominic P. BEHAN and Derek T. CHALMERS
Serial No: 09/060,188
Filed: April 14, 1998
For: *A Method of Identifying Modulators of Cell Surface Membrane Receptors Useful in the Treatment of Disease*
Attorney's Docket: 3086-9
Examiner:
Group Art No:

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Honorable Commissioner of Patents and Trademarks, Washington D.C. 20231 on July 8, 1998.


Suzannah K. Sundby
Patent Agent for the Applicants
USPTO Reg. No. P-43,172

U.S. PATENT DOCUMENTS

Examiner's Initials	Cite No.		T ²
		NA	

Examiner Signature	Date Considered
--------------------	-----------------

OTHER DOCUMENTS – NON-PATENT LITERATURE DOCUMENTS

Examiner's Initials	Cite No.		T ²
		ALLA, S.A., et al (1996). Extracellular domains of the bradykinin B2 receptor involved in ligand binding and agonist sensing defined by anti-peptide antibodies. <i>J. Biol. Chem.</i> , 271, 1748-1755.	
		ADVENIER, C. et al (1992). Effects on the isolated human bronchus of SR 48968, a potent and selective nonpeptide antagonist of the neurokinin A (NK2) receptors. <i>Am. Rev. Respir. Dis.</i> , 146:5 Pt 1, 1177-81.	
		ALEXANDER, W.S., et al (1995). Point mutations within the dimer interface homology domain of c-Mpl induce constitutive receptor activity and tumorigenicity. <i>EMBO J.</i> , 14, 5569-78.	

Examiner Signature	Date Considered
--------------------	-----------------

	ARVANITIKIS, L., et al (1997). Human herpesvirus KSHV encodes a constitutively active G-protein-coupled receptor linked to cell proliferation. <i>Nature</i> , 385, 347-349.	
	BARKER, E.L., et al (1994). Constitutively active 5-hydroxytryptamine 2C receptors reveal novel inverse agonist activity of receptor ligands. <i>J. Biol. Chem.</i> , 269:16, 11687-11690.	
	BAXTER, G. (1995). 5-HT ₂ receptors: a family re-united? <i>Trends Pharmacol. Sci.</i> 16, 105-110.	
	BESMER, P., et al (1986). A new acute transforming feline retrovirus and relationship of its oncogene v-kit with the protein kinase gene family. <i>Nature</i> , 320, 415.	
	BLIN, N., et al (1995). Mapping of single amino acid residues required for selective activation of Gq/11 by the m3 muscarinic acetylcholine receptor. <i>J. Biol. Chem.</i> , 270, 17741-17748.	
	BOND, R. A., & BOUVIER, M., (1998). Inverse agonists and G-protein-coupled receptors. <i>Receptor-Based Drug Design</i> . Ed. Paul Leff. New York; M. Dekker. 363-377.	
	BOONE, C., et al (1993). Mutations that alter the third cytoplasmic loop of the a-factor receptor lead to a constitutive and hypersensitive phenotype. <i>Proc. Natl. Acad. Sci. (USA)</i> , 90:21, 9921-5.	
	BURSTEIN, E.S., et al (1996). Constitutive activation of chimeric m2/m5 muscarinic receptors and delineation of G-protein coupling selectivity domains. <i>Biochem Pharmacol</i> , 51:4, 539-44.	
	BURSTEIN, E.S., et al (1996). Amino acid side chains that define muscarinic receptor/G-protein coupling. Studies of the third intracellular loop. <i>J. Biol. Chem.</i> , 271:6, 2882-5.	
	BURSTEIN, E.S., et al (1995). Constitutive activation of muscarinic receptors by the G-protein Gq. <i>FEBS Lett.</i> , 363:3, 261-3.	
	BYLUND, D. (1994). International union of pharmacology nomenclature of adrenoceptors. <i>Pharmacol. Review.</i> , 46, 121-136.	
	CASEY, C., et al (1996). Constitutively active mutant 5-HT _{2A} serotonin receptors: inverse agonist activity of classical 5HT _{2A} antagonists. <i>Soc. Neurosci. Abstracts</i> # 699.10	
	CHEATHAM, B., et al (1993). Substitution of the erb-2 oncoprotein transmembrane domain activates the insulin receptor and modulates the action of insulin-receptor substrate. <i>Proc. Natl. Acad. Sci. (USA)</i> , 90, 7336-73340.	
	CHEN, T.S. et al (1993). Microbial hydroxylation and glucuronidation of the angiotensin II (AII) receptor antagonist MK 954. <i>J. Antibiot. (Tokyo)</i> , 46:1, 131-4.	
	CHEN, W., et al (1995). A colorimetric assay for measuring activation of G _s – and G _q – coupled signalling pathways. <i>Anal. Biochem.</i> , 226:2, 349-354.	
	CHIDLAC, P., et al (1994). Inverse agonist activity of beta-adrenergic antagonists. <i>J. Pharm. Expt. Ther.</i> , 45, 490-499.	

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

		CLOZEL, M. et al (1993). In vivo pharmacology of Ro 46-2005, the first synthetic nonpeptide endothelin receptor antagonist: implications for endothelin physiology. <i>J. Cardiovasc. Pharmacol.</i> , 22 Suppl 8:, S377-9.	
		COLLESI, C., et al (1996). A splicing variant of the RON transcript induces constitutive tyrosine kinase activity and an invasive phenotype. <i>Mol. & Cellular Biol.</i> , 16, 5518-5526.	
		COOPER, C.S., et al (1984). Molecular cloning of a new transforming gene from a chemically transformed human cell line. <i>Nature</i> , 311, 29-33.	
		DESBLOS-MOUTHON, C. et al (1996). Deletion of Asn281 in the -su b unit of the human insulin receptor causes constitutive activation of the receptor and insulin desensitization. <i>J. Clin. Endocrinol. Metab.</i> , 81, 719-727.	
		DI RENZO, M.F., et al (1991). Expression of the Met/HGF receptor in normal and neoplastic human. <i>Oncogene</i> , 6:11, 1997-2003.	
		DI RENZO, M.F., et al (1992). Overexpression of the c-Met/HGF receptor gene in human thyroid carcinomas. <i>Oncogene</i> , 7, 2549-2553.	
		DUPREZ, L., et al (1994). Germline mutations in the thyrotropin receptor gene cause non-autoimmune autosomal dominant hyperthyroidism. <i>Nature Genetics</i> , 7, 396-401.	
		EGGERICKX, D., et al (1995). Molecular cloning of an orphan G-protein-coupled receptor that constitutively activates adenylate cyclase. <i>Biochem. J.</i> , 389, 837-843.	
		EVANS, B.E. et al (1992). Orally active, nonpeptide oxytocin antagonists. <i>J. Med. Chem.</i> , 35:21, 3919-27.	
		FU, M., et al (1994). Functional autoimmune epitope on alpha1-adrenergic receptors in patients with malignant hypertension. <i>Lancet</i> , 344, 1660-1663.	
		FURITSU, T., et al (1993). Identification of mutations in the coding sequence of the proto-oncogene c-kit in a human mast cell leukemia cell line causing ligand-independent activation of c-kit product. <i>J. Clin. Invest.</i> , 92, 1736.	
		GELLAI, M. et al (1995). Nonpeptide endothelin receptor antagonists. V: Prevention and reversal of acute renal failure in the rat by SB 209670. <i>J. Pharmacol. Exp. Ther.</i> , 275:1, 200-6.	
		GITTER, B.D. et al (1995). Pharmacological characterization of LY303870: a novel, potent and selective nonpeptide substance P (neurokinin-1) receptor antagonist. <i>J. Pharmacol. Exp. Ther.</i> , 275:2, 737-44.	
		GOUILLEUX-GRUART, V., (1996). STAT-related transcription factors are constitutively activated in peripheral blood cells from acute leukemia patients. <i>Blood</i> , 87:5, 1692-7.	
		HANSSON, J.H., et al (1995). Hypertension caused by a truncated epithelial sodium channel gamma subunit: genetic heterogeneity of Liddle syndrome. <i>Nat. Genet.</i> , 11:1, 76-82.	
		HASEGAWA, H., et al (1996). Two isoforms of the prostaglandin E receptor EP3 subtype different in agonist-independent constitutive activity. <i>J. Biol. Chem.</i> , 271:4, 1857-1860.	

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

		HENDLER, A.M. & OZANNE, B.W. (1984). Human squamous cell lung cancers express increased epidermal growth factor receptors. J. Clin. Invest., 74, 647-651.	
		HERRICK-DAVIS, K., et al (1996). Constitutively active 5HT _{2C} serotonin receptor created by site directed mutagenesis. Soc. Neuroscience abstract #699.18.	
		HIEBLE, J. (1995). International union of pharmacology. X. Recommendation for nomenclature of β_1 -adrenoceptors. Pharmacol. Review., 47, 267-270.	
		HILL, S. (1990). Distribution properties and functional characteristics of three classes of histamine receptor. Pharmacol. Review. 7, 1-51.	
		HOGGER, P. et al (1995). Activating and inactivating mutations in the N- and C-terminal I3 loop junctions of muscarinic acetylcholine Hm1 receptors. J. Biol. Chem., 270, 7405-7410.	
		IKEDA, H., et al (1991). Expression and functional role of the proto-oncogen c-kit in acute myeloblastic leukemia cells. Blood, 78, 2962.	
		IMURA, R. et al (1992). Inhibition by HS-142-1, a novel nonpeptide atrial natriuretic peptide antagonist of microbial origin, of atrial natriuretic peptide-induced relaxation of isolated rabbit aorta through the blockade of guanylyl cyclase-linked receptors. Mol. Pharmacol., 42:6, 982-90.	
		JAKUB/EIK, J., et al (1995). Constitutive activity of the M1-M4 subtypes of muscarinic receptors in transfected CHO cells and of muscarinic receptors in the heart cells revealed by negative antagonists. FEBS Lett, 377:2, 275-9.	
		KJELSBORG, M.A., et al (1992). Constitutive activation of the alpha 1B-adrenergic receptor by all amino acid substitutions at a single site. J. Biol. Chem., 267, 1430-1433.	
		KNAPP, R. (1995). Molecular biology and pharmacology of cloned opioid receptors. FASEB J. 9, 516-525.	
		KOSUGI, S., et al (1995). Characterization of heterogenous mutations causing constitutive activation of the luteinizing hormone receptor in familial male precocious puberty. Human Molecular Genetics, 4:2, 183-188.	
		KOSUGI, S., et al (1993). Identification of thyroid-stimulating antibody-specific interaction sites in the N-terminal region of the thyrotropin receptor. Molecular Endocrinology, 7, 114-130.	
		KRAUS, M.H., et al (1993). Demonstration of ligand-independent signalling by the erbB-3 tyrosine kinase and its constitutive activation in human breast tumor cells. Proc. Natl. Acad. Sci. (USA), 90, 2900-4.	
		KUDLACZ, E.M. et al (1996). In vitro and in vivo characterization of MDL 105,212A, a nonpeptide NK-1/NK-2 tachykinin receptor antagonist. J. Pharmacol. Exp. Ther., 277:2, 840-51.	
		KURIU, A., et al (1991). Proliferation of human myeloid leukemia cell line associated with the tyrosine phosphorylation and activation of the proto-oncogene c-kit product. Blood, 78, 2834.	

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

	LABBE-JULLIE, C. (1994). Effect of the nonpeptide neurotensin antagonist, SR 48692, and two enantiomeric analogs, SR 48527 and SR 49711, on neurotensin binding and contractile responses in guinea pig ileum and colon. <i>J. Pharmacol. Exp. Ther.</i> , 271:1, 267-76.	
	LATRONICO, A.C., et al (1995). A novel mutation of the luteinizing hormone receptor gene causing male gonadotropin-independent precocious puberty. <i>J. Clin. Endocrinol. Metab.</i> , 80, 2490-2494.	
	LAUE, L., et al (1995). Genetic heterogeneity of constitutively activating mutations of the human luteinizing hormone receptor in familial male-limited precocious puberty. <i>Proc. Natl. Acad. Sci. (USA)</i> , 92, 1906-1910.	
	LØVLIE, R., et al (1996). The Ca(2+)-sensing receptor gene (PCAR1) mutation T151M in isolated autosomal dominant hypoparathyroidism. <i>Hum. Genet.</i> , 98:2, 129-33.	
	LEFKOWITZ, R., et al (1993). Constitutive activity of receptors coupled to guanine nucleotide regulatory proteins. <i>Trends Pharmacol. Sci.</i> , 14, 300-307.	
	LIBERMANN, T.A., et al (1985). Amplification, enhanced expression and possible rearrangement of EGF receptor gene in primary human brain tumors of glial origin. <i>Nature</i> , 313, 144-147.	
	LIU, C., et al (1992). Overexpression of c-met proto-oncogene but not epidermal growth factor receptor or c-erbB-2 in primary human colorectal carcinomas. <i>Oncogene</i> , 7:1, 181-185.	
	LIU, J., et al (1996). Molecular mechanisms involved in muscarinic acetylcholine receptor-mediated G protein activation studied by insertion mutagenesis. <i>J. Biol. Chem.</i> , 271:11, 6172-6178.	
	LONARDO, F., et al (1990). The normal erb-2 product is an atypical receptor-like tyrosine kinase with constitutive activity in the absence of ligand. <i>The new Biologist</i> , 2:11, 992-1003.	
	MAENHAUT, C., et al (1990). RCD8 codes for an adenosine A2 receptor with physiological constitutive activity. <i>Biochem. Biophys. Res. Com.</i> , 173:3, 1169-1178.	
	MANN, J., et al (1986). Increased serotonin ₂ and beta-adrenergic receptor binding in the frontal cortices of suicide victims. <i>Arch. Gen. Psychiat.</i> 43, 954-959.	
	MARTONE, R.L. et al (1996). Human CRF receptor chimeras: mapping of ligand binding determinants. Abstract 609.8. 26 th meeting for the society of neuroscience, Washington, D.C., November 16-21, 1996.	
	MAGNUSSON, Y., et al (1994). Autoimmunity in idiopathic dilated cardiomyopathy. <i>Circulation</i> , 89, 2760-2767.	
	MATUS-LEIBOVITCH, N., et al (1995). Truncation of the thyrotropin-releasing hormone receptor carboxy tail causes constitutive activity and leads to impaired responsiveness in <i>Xenopus</i> oocytes and AtT20 cells. <i>J. Biol. Chem.</i> , 270:3, 1041-1047.	

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

	MYLES, G.M., et al (1994). Tyrosine 569 in the c-fms juxtamembrane domain is essential for kinase activity and macrophage colony-stimulating factor-dependent internalization. <i>Mol. Cell. Biol.</i> , 14, 4843.	
	NANEVICZ, T., et al (1996). Thrombin receptor activating mutations. <i>J. Biol. Chem.</i> , 271, 702-706.	
	NATALI, P.G., et al (1993). Expression of the c-Met/HGF receptor in human melanocytic neoplasms: demonstration of the relationship to malignant melanoma tumor progression. <i>Br. J. Cancer</i> , 68:4, 746-750.	
	NEILSON, K.M., et al (1995). Constitutive activation of fibroblast growth factor receptor-2 by a point mutation associated with Crouzon syndrome. <i>J. Biol. Chem.</i> , 270:44, 26037-26040.	
	ODA, S. et al (1992). Pharmacological profile of HS-142-1, a novel nonpeptide atrial natriuretic peptide (ANP) antagonist of microbial origin. II. Restoration by HS-142-1 of ANP-induced inhibition of aldosterone production in adrenal glomerulosa cells. <i>J. Pharmacol. Exp. Ther.</i> , 263:1, 241-5.	
	O'DOWD, B.F., et al (1988). Site-directed mutagenesis of the cytoplasmic domains of the human BETA ₂ -adrenergic receptor. <i>J. Biol. Chem.</i> , 263, 15985-15992.	
	PALKOWITZ, A.D. et al (1994). Structural evolution and pharmacology of a novel series of triacid angiotensin II receptor antagonists. <i>J. Med. Chem.</i> , 37:26, 4508-21.	
	PARENT, J., et al (1996). Mutations of two adjacent amino acids generate inactive and constitutively active forms of the human platelet-activating factor receptor. <i>J. Biol. Chem.</i> , 271:14, 7949-7955.	
	PARFITT, A.M., et al (1996). Hypercalcemia due to constitutive activity of the parathyroid hormone (PTH)/PTH-related peptide receptor: comparison with primary hyperparathyroidism. <i>J. Clin. Endocr. Metab.</i> , 81, 3584-3588.	
	PARMA, J., et al (1993). Somatic mutations in the thyrotropin receptor gene cause hyperfunctioning thyroid adenomas. <i>Nature</i> , 365, 649-651.	
	PEI, G., et al (1994). A constitutive active mutant BETA ₂ -adrenergic receptor is constitutively desensitized and phosphorylated. <i>Proc. Natl. Acad. Sci. (USA)</i> , 91, 2699-2702.	
	PENDLEY, C.E. et al (1993). The gastrin/cholecystokinin-B receptor antagonist L-365,260 reduces basal acid secretion and prevents gastrointestinal damage induced by aspirin, ethanol and cysteamine in the rat. <i>J Pharmacol Exp Ther</i> , 265:3, 1348-54.	
	PEROUTKA, S. (1995). Serotonin receptor subtypes. Their evolution and clinical relevance. <i>CNS Drugs</i> . 4, 19-28.	
	PETTIBONE, D.J. & CLINESCHMIDT, B.V. (1993). Development and pharmacological assessment of novel peptide and nonpeptide oxytocin antagonists. <i>Regul Pept</i> , 29, 45:1-2.	

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

	PRAT, M.P., et al (1991). The receptor encoded by the human C-MET oncogene is expressed in hepatocytes, epithelial cells and solid tumors. <i>Int. J. Cancer</i> , 49, 323-328.	
	PREZEAU, L., et al (1996). Changes in the carboxy-terminal domain of metabotropic glutamate receptor 1 by alternate splicing generate receptors with differing agonist-independent activity. <i>Mol. Pharmacol.</i> , 49, 422-429.	
	RAKOVSKA, A. et al (1993). Effect of loxiglumide (CR 1505) on CCK-induced contractions and 3H-acetylcholine release from guinea-pig gallbladder. <i>Neuropeptides</i> , 25:5, 271-6.	
	De Dios, I. & Manso, M.A. (1994). Effect of L-364,718 (CCK receptor antagonist) on exocrine pancreatic secretion of hydrocortisone-treated rats. <i>Pancreas</i> , 9:2, 212-8.	
	REN, Q., et al (1993). Constitutive active mutants of the ALPHA ₂ -adrenergic receptor. <i>J. Biol. Chem.</i> , 268, 16483-16487.	
	REYNOLDS, E.E. (1995). Pharmacological characterization of PD 156707, an orally active ETA receptor antagonist. <i>J. Pharmacol. Exp. Ther.</i> , 273:3, 1410-7.	
	ROBBINS, L.S., et al (1993). Pigmentation phenotypes of variant extension locus alleles result from point mutations that alter MSH receptor function. <i>Cell</i> , 72, 827-834.	
	RONG, S., et al (1993). Met expression and sarcoma tumorigenicity. <i>Cancer Res.</i> , 53:22, 5355-60.	
	SAMAMA, P., et al (1993a). A mutation-induced activation state of the B2-adrenergic receptor. <i>J. Biol. Chem.</i> , 268:7, 4625-36.	
	SAUTEL, M. et al (1996). Neuropeptide Y and the nonpeptide antagonist BIBP 3226 share an overlapping binding site at the human Y1 receptor. <i>Mol. Pharmacol.</i> , 50:2, 285-92.	
	SAWUTZ, D.G. et al (1995). Pharmacology and structure—activity relationships of the nonpeptide bradykinin receptor antagonist WIN 64338. <i>Can. J. Physiol. Pharmacol.</i> , 73:7, 805-11.	
	SCHEER, A. & COTECCHIA, S., (1997). Constitutively active G protein-coupled receptors: potential mechanisms of receptor activation. <i>J. Receptor & Signal Transduction Research</i> , 17(1-3), 57-73.	
	SCHEER, A., et al (1997). The activation process of the 1B-adrenergic receptor: potential role of protonation and hydrophobicity of a highly conserved aspartate. <i>Proc. Natl. Acad. Sci. (USA)</i> , 94, 808-813.	
	SCHWINN, D.A., et al (1995). Cloning and pharmacological characterization of human Alpha-1 adrenergic receptors: sequence corrections and direct comparison with other species homologues. <i>The J. Pharmacol.</i> , 272, 134-142.	
	SCHILD, L., et al (1995). A mutation in the epithelial sodium channel causing Liddle disease increases channel activity in the <i>Xenopus laevis</i> oocyte expression system. <i>Proc. Natl. Acad. Sci. (USA)</i> , 92, 5699-703.	
	SEEMAN, P. & VAN TOL, H. (1994). Dopamine receptor pharmacology. <i>Trends Pharmacol. Sci.</i> 15, 264-270.	

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

	SEEMAN, P. (1993). Dopamine D4 receptors elevated in schizophrenia. <i>Nature</i> , 365, 441-445.	
	SERRADEIL-LE GAL, C., et al (1993). Biochemical and pharmacological properties of SR 49059, a new, potent, nonpeptide antagonist of rat and human vasopressin V1a receptors. <i>J. Clin. Invest.</i> , 92:1, 224-31.	
	SHARIF, M., et al (1994). Malignant transformation by G protein-coupled hormone receptors. <i>Molecular & Cellular Endocrinology</i> , 100, 115-119.	
	SHOWERS, M.O., et al (1992). Activation of the erythropoietin receptor by the Friend spleen focus-forming virus gp55 glycoprotein induces constitutive protein tyrosine phosphorylation. <i>Blood</i> , 80, 3070-8.	
	SKINNER, R.H., et al (1994). Direct measurement of the binding of Ras to neurofibromin using scintillation proximity assay. <i>Anal. Biochem.</i> , 223, 259-265.	
	SLAMON, D.J., et al (1987). Human breast cancer: correlation of relapse and survival with amplification of the HER-2 neu oncogene. <i>Science</i> , 235, 177-182.	
	SLAMON, D.J., et al (1989). Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. <i>Science</i> , 244, 707-712.	
	SOLOMON, Y., et al (1974). A highly sensitive adenylate cyclase assay. <i>Anal. Biochem.</i> , 58, 541-548.	
	SPIEGEL, A.M., et al (1995). Defects in G protein-coupled signal transduction in human disease. <i>Ann. Rev. Physiol.</i> , 58, 143-170.	
	TER LACK, A., et al (1995). Modelling and mutation studies on the histamine H1-receptor agonist binding site reveal different binding modes for H1-agonists: Asp116 (TM3) has a constitutive role in receptor stimulation. <i>J. Computer-aided molecular design</i> , 9, 319-330.	
	TIBERI, M. & CARON, M.G. (1994). High agonist-independent activity is a distinguishing feature of the dopamine D1B receptor subtype. <i>The J. Biol. Chem.</i> 269:45. 27925-27931.	
	TSUJIMURA, T., et al (1996). Constitutive activation of c-kit in FMA3 murine mastocytoma cells caused by a deletion of seven amino acids at the juxtamembrane domain. <i>Blood</i> , 87, 273-283.	
	WANG, Z., et al (1994). Constitutive opioid receptor activation as a regulatory mechanism underlying narcotic tolerance and dependence. <i>Life Sciences</i> , 54:22, 339-350.	
	WATOWICH, S.S., et al (1992). Homodimerization and constitutive activation of the erythropoietin receptor. <i>Proc. Natl. Acad. Sci. (USA)</i> , 89, 2140-4.	
	WEBER-NORDT, R.M., et al (1996). Constitutive activation of STAT proteins in primary lymphoid and myeloid leukemia cells and in Epstein-Barr virus (EBV)-related lymphoma cell lines. <i>Blood</i> , 88:3, 809-16.	
	WEBSTER, K. & DONOGHUE, J. (1996). Constitutive activation of fibroblast growth factor receptor 3 by the transmembrane point mutation found in achondroplasia. <i>The EMBO J.</i> , 15, 520-527.	

Examiner Signature	Date Considered	
-----------------------	--------------------	--

		XU, Y.H., et al (1984). Characterization of epidermal growth factor receptor gene expression in malignant and normal human cell lines. Proc. Natl .Acad. Sci. (USA)., 81, 7308-7312.	
		YAMADA, K., et al (1992). Substitution of the insulin receptor transmembrane domain with the c-neu/erb2 transmembrane domain constitutively activates the insulin receptor tyrosine kinase in vitro. J. Biol. Chem., 267, 12452-12461.	
		ZHEN, Z., et al (1994). Structural and functional domains critical for constitutive activation of the HGF-receptor (<i>Met</i>).Oncogene, 9, 1691-1697.	

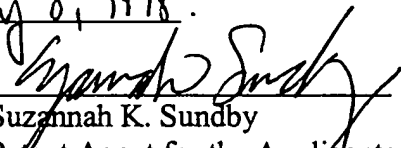
Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

INFORMATION DISCLOSURE STATEMENT

COPY

In re Application of: Dominic P. BEHAN and Derek T. CHALMERS
 Serial No: 09/060,188
 Filed: April 14, 1998
 For: *A Method of Identifying Modulators of Cell Surface Membrane Receptors Useful in the Treatment of Disease*
 Attorney's Docket: 3086-9
 Examiner:
 Group Art No:

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Honorable Commissioner of Patents and Trademarks, Washington D.C. 20231 on July 8, 1998.


 Suzannah K. Sundby
 Patent Agent for the Applicants
 USPTO Reg. No. P-43,172

U.S. PATENT DOCUMENTS

Examiner's Initials	Cite No.		T ²
		NA	

Examiner Signature	Date Considered

OTHER DOCUMENTS – NON-PATENT LITERATURE DOCUMENTS

Examiner's Initials	Cite No.		T ²
		ALLA, S.A., et al (1996). Extracellular domains of the bradykinin B2 receptor involved in ligand binding and agonist sensing defined by anti-peptide antibodies. J. Biol. Chem., 271, 1748-1755.	
		ADVENIER, C. et al (1992). Effects on the isolated human bronchus of SR 48968, a potent and selective nonpeptide antagonist of the neurokinin A (NK2) receptors. Am. Rev. Respir. Dis., 146:5 Pt 1, 1177-81.	
		ALEXANDER, W.S., et al (1995). Point mutations within the dimer interface homology domain of c-Mpl induce constitutive receptor activity and tumorigenicity. EMBO J., 14, 5569-78.	

Examiner Signature	Date Considered

	ARVANITIKIS, L., et al (1997). Human herpesvirus KSHV encodes a constitutively active G-protein-coupled receptor linked to cell proliferation. <i>Nature</i> , 385, 347-349.	
	BARKER, E.L., et al (1994). Constitutively active 5-hydroxytryptamine 2C receptors reveal novel inverse agonist activity of receptor ligands. <i>J. Biol. Chem.</i> , 269:16, 11687-11690.	
	BAXTER, G. (1995). 5-HT ₂ receptors: a family re-united? <i>Trends Pharmacol. Sci.</i> 16, 105-110.	
	BESMER, P., et al (1986). A new acute transforming feline retrovirus and relationship of its oncogene v-kit with the protein kinase gene family. <i>Nature</i> , 320, 415.	
	BLIN, N., et al (1995). Mapping of single amino acid residues required for selective activation of Gq/11 by the m3 muscarinic acetylcholine receptor. <i>J. Biol. Chem.</i> , 270, 17741-17748.	
	BOND, R. A., & BOUVIER, M., (1998). Inverse agonists and G-protein-coupled receptors. <i>Receptor-Based Drug Design</i> . Ed. Paul Leff. New York; M. Dekker. 363-377.	
	BOONE, C., et al (1993). Mutations that alter the third cytoplasmic loop of the a-factor receptor lead to a constitutive and hypersensitive phenotype. <i>Proc. Natl. Acad. Sci. (USA)</i> , 90:21, 9921-5.	
	BURSTEIN, E.S., et al (1996). Constitutive activation of chimeric m2/m5 muscarinic receptors and delineation of G-protein coupling selectivity domains. <i>Biochem Pharmacol</i> , 51:4, 539-44.	
	BURSTEIN, E.S., et al (1996). Amino acid side chains that define muscarinic receptor/G-protein coupling. Studies of the third intracellular loop. <i>J. Biol. Chem.</i> , 271:6, 2882-5.	
	BURSTEIN, E.S., et al (1995). Constitutive activation of muscarinic receptors by the G-protein Gq. <i>FEBS Lett.</i> , 363:3, 261-3.	
	BYLUND, D. (1994). International union of pharmacology nomenclature of adrenoceptors. <i>Pharmacol. Review.</i> , 46, 121-136.	
	CASEY, C., et al (1996). Constitutively active mutant 5-HT _{2A} serotonin receptors: inverse agonist activity of classical 5HT _{2A} antagonists. <i>Soc. Neurosci. Abstracts</i> # 699.10	
	CHEATHAM, B., et al (1993). Substitution of the erb-2 oncoprotein transmembrane domain activates the insulin receptor and modulates the action of insulin-receptor substrate. <i>Proc. Natl. Acad. Sci. (USA)</i> , 90, 7336-73340.	
	CHEN, T.S. et al (1993). Microbial hydroxylation and glucuronidation of the angiotensin II (AII) receptor antagonist MK 954. <i>J. Antibiot. (Tokyo)</i> , 46:1, 131-4.	
	CHEN, W., et al (1995). A colorimetric assay for measuring activation of G _s - and G _q - coupled signalling pathways. <i>Anal. Biochem.</i> , 226:2, 349-354.	
	CHIDIAC, P., et al (1994). Inverse agonist activity of beta-adrenergic antagonists. <i>J. Pharm. Expt. Ther.</i> , 45, 490-499.	

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

		CLOZEL, M. et al (1993). In vivo pharmacology of Ro 46-2005, the first synthetic nonpeptide endothelin receptor antagonist: implications for endothelin physiology. <i>J. Cardiovasc. Pharmacol.</i> , 22 Suppl 8:, S377-9.	
		COLLESI, C., et al (1996). A splicing variant of the RON transcript induces constitutive tyrosine kinase activity and an invasive phenotype. <i>Mol. & Cellular Biol.</i> , 16, 5518-5526.	
		COOPER, C.S., et al (1984). Molecular cloning of a new transforming gene from a chemically transformed human cell line. <i>Nature</i> , 311, 29-33.	
		DESBIOS-MOUTHON, C. et al (1996). Deletion of Asn281 in the -su b unit of the human insulin receptor causes constitutive activation of the receptor and insulin desensitization. <i>J. Clin. Endocrinol. Metab.</i> , 81, 719-727.	
		DI RENZO, M.F., et al (1991). Expression of the Met/HGF receptor in normal and neoplastic human. <i>Oncogene</i> , 6:11, 1997-2003.	
		DI RENZO, M.F., et al (1992). Overexpression of the c-Met/HGF receptor gene in human thyroid carcinomas. <i>Oncogene</i> , 7, 2549-2553.	
		DUPREZ, L., et al (1994). Germline mutations in the thyrotropin receptor gene cause non-autoimmune autosomal dominant hyperthyroidism. <i>Nature Genetics</i> , 7, 396-401.	
		EGGERICKX, D., et al (1995). Molecular cloning of an orphan G-protein-coupled receptor that constitutively activates adenylate cyclase. <i>Biochem. J.</i> , 389, 837-843.	
		EVANS, B.E. et al (1992). Orally active, nonpeptide oxytocin antagonists. <i>J. Med. Chem.</i> , 35:21, 3919-27.	
		FU, M., et al (1994). Functional autoimmune epitope on alpha1-adrenergic receptors in patients with malignant hypertension. <i>Lancet</i> , 344, 1660-1663.	
		FURITSU, T., et al (1993). Identification of mutations in the coding sequence of the proto-oncogene c-kit in a human mast cell leukemia cell line causing ligand-independent activation of c-kit product. <i>J. Clin. Invest.</i> , 92, 1736.	
		GELLAI, M. et al (1995). Nonpeptide endothelin receptor antagonists. V: Prevention and reversal of acute renal failure in the rat by SB 209670. <i>J. Pharmacol. Exp. Ther.</i> , 275:1, 200-6.	
		GITTER, B.D. et al (1995). Pharmacological characterization of LY303870: a novel, potent and selective nonpeptide substance P (neurokinin-1) receptor antagonist. <i>J. Pharmacol. Exp. Ther.</i> , 275:2, 737-44.	
		GOUILLEUX-GRUART, V., (1996). STAT-related transcription factors are constitutively activated in peripheral blood cells from acute leukemia patients. <i>Blood</i> , 87:5, 1692-7.	
		HANSSON, J.H., et al (1995). Hypertension caused by a truncated epithelial sodium channel gamma subunit: genetic heterogeneity of Liddle syndrome. <i>Nat. Genet.</i> , 11:1, 76-82.	
		HASEGAWA, H., et al (1996). Two isoforms of the prostaglandin E receptor EP3 subtype different in agonist-independent constitutive activity. <i>J. Biol. Chem.</i> , 271:4, 1857-1860.	

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

		HENDLER, A.M. & OZANNE, B.W. (1984). Human squamous cell lung cancers express increased epidermal growth factor receptors. J. Clin. Invest., 74, 647-651.	
		HERRICK-DAVIS, K., et al (1996). Constitutively active 5HT _{2C} serotonin receptor created by site directed mutagenesis. Soc. Neuroscience abstract #699.18.	
		HIEBLE, J. (1995). International union of pharmacology. X. Recommendation for nomenclature of 1-adrenoceptors. Pharmacol. Review., 47, 267-270.	
		HILL, S. (1990). Distribution properties and functional characteristics of three classes of histamine receptor. Pharmacol. Review. 7, 1-51.	
		HOGGER, P. et al (1995). Activating and inactivating mutations in the N- and C-terminal I3 loop junctions of muscarinic acetylcholine Hm1 receptors. J. Biol. Chem., 270, 7405-7410.	
		IKEDA, H., et al (1991). Expression and functional role of the proto-oncogen c-kit in acute myeloblastic leukemia cells. Blood, 78, 2962.	
		IMURA, R. et al (1992). Inhibition by HS-142-1, a novel nonpeptide atrial natriuretic peptide antagonist of microbial origin, of atrial natriuretic peptide-induced relaxation of isolated rabbit aorta through the blockade of guanylyl cyclase-linked receptors. Mol. Pharmacol., 42:6, 982-90.	
		JAKUB/EIK, J., et al (1995). Constitutive activity of the M1-M4 subtypes of muscarinic receptors in transfected CHO cells and of muscarinic receptors in the heart cells revealed by negative antagonists. FEBS Lett, 377:2, 275-9.	
		KJELSBORG, M.A., et al (1992). Constitutive activation of the alpha 1B-adrenergic receptor by all amino acid substitutions at a single site. J. Biol. Chem., 267, 1430-1433.	
		KNAPP, R. (1995). Molecular biology and pharmacology of cloned opioid receptors. FASEB J. 9, 516-525.	
		KOSUGI, S., et al (1995). Characterization of heterogenous mutations causing constitutive activation of the luteinizing hormone receptor in familial male precocious puberty. Human Molecular Genetics, 4:2, 183-188.	
		KOSUGI, S., et al (1993). Identification of thyroid-stimulating antibody-specific interaction sites in the N-terminal region of the thyrotropin receptor. Molecular Endocrinology, 7, 114-130.	
		KRAUS, M.H., et al (1993). Demonstration of ligand-independent signalling by the erbB-3 tyrosine kinase and its constitutive activation in human breast tumor cells. Proc. Natl. Acad. Sci. (USA), 90, 2900-4.	
		KUDLACZ, E.M. et al (1996). In vitro and in vivo characterization of MDL 105,212A, a nonpeptide NK-1/NK-2 tachykinin receptor antagonist. J. Pharmacol. Exp. Ther., 277:2, 840-51.	
		KURIU, A., et al (1991). Proliferation of human myeloid leukemia cell line associated with the tyrosine phosphorylation and activation of the proto-oncogene c-kit product. Blood, 78, 2834.	

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

	LABBE-JULLIE, C. (1994). Effect of the nonpeptide neurotensin antagonist, SR 48692, and two enantiomeric analogs, SR 48527 and SR 49711, on neurotensin binding and contractile responses in guinea pig ileum and colon. <i>J. Pharmacol. Exp. Ther.</i> , 271:1, 267-76.	
	LATRONICO, A.C., et al (1995). A novel mutation of the luteinizing hormone receptor gene causing male gonadotropin-independent precocious puberty. <i>J. Clin. Endocrinol. Metab.</i> , 80, 2490-2494.	
	LAUE, L., et al (1995). Genetic heterogeneity of constitutively activating mutations of the human luteinizing hormone receptor in familial male-limited precocious puberty. <i>Proc. Natl. Acad. Sci. (USA)</i> , 92, 1906-1910.	
	LØVLIE, R., et al (1996). The Ca(2+)-sensing receptor gene (PCAR1) mutation T151M in isolated autosomal dominant hypoparathyroidism. <i>Hum. Genet.</i> , 98:2, 129-33.	
	LEFKOWITZ, R., et al (1993). Constitutive activity of receptors coupled to guanine nucleotide regulatory proteins. <i>Trends Pharmacol. Sci.</i> , 14, 300-307.	
	LIBERMANN, T.A., et al (1985). Amplification, enhanced expression and possible rearrangement of EGF receptor gene in primary human brain tumors of glial origin. <i>Nature</i> , 313, 144-147.	
	LIU, C., et al (1992). Overexpression of c-met proto-oncogene but not epidermal growth factor receptor or c-erbB-2 in primary human colorectal carcinomas. <i>Oncogene</i> , 7:1, 181-185.	
	LIU, J., et al (1996). Molecular mechanisms involved in muscarinic acetylcholine receptor-mediated G protein activation studied by insertion mutagenesis. <i>J. Biol. Chem.</i> , 271:11, 6172-6178.	
	LONARDO, F., et al (1990). The normal erb-2 product is an atypical receptor-like tyrosine kinase with constitutive activity in the absence of ligand. <i>The new Biologist</i> , 2:11, 992-1003.	
	MAENHAUT, C., et al (1990). RCD8 codes for an adenosine A2 receptor with physiological constitutive activity. <i>Biochem. Biophys. Res. Com.</i> , 173:3, 1169-1178.	
	MANN, J., et al (1986). Increased serotonin ₂ and beta-adrenergic receptor binding in the frontal cortices of suicide victims. <i>Arch. Gen. Psychiat.</i> 43, 954-959.	
	MARTONE, R.L. et al (1996). Human CRF receptor chimeras: mapping of ligand binding determinants. Abstract 609.8. 26 th meeting for the society of neuroscience, Washington, D.C., November 16-21, 1996.	
	MAGNUSSON, Y., et al (1994). Autoimmunity in idiopathic dilated cardiomyopathy. <i>Circulation</i> , 89, 2760-2767.	
	MATUS-LEIBOVITCH, N., et al (1995). Truncation of the thyrotropin-releasing hormone receptor carboxy tail causes constitutive activity and leads to impaired responsiveness in <i>Xenopus</i> oocytes and AtT20 cells. <i>J. Biol. Chem.</i> , 270:3, 1041-1047.	

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

	MYLES, G.M., et al (1994). Tyrosine 569 in the c-fms juxtamembrane domain is essential for kinase activity and macrophage colony-stimulating factor-dependent internalization. Mol. Cell. Biol., 14, 4843.	
	NANEVICZ, T., et al (1996). Thrombin receptor activating mutations. J. Biol. Chem., 271, 702-706.	
	NATALI, P.G., et al (1993). Expression of the c-Met/HGF receptor in human melanocytic neoplasms: demonstration of the relationship to malignant melanoma tumor progression. Br. J. Cancer, 68:4, 746-750.	
	NEILSON, K.M., et al (1995). Constitutive activation of fibroblast growth factor receptor-2 by a point mutation associated with Crouzon syndrome. J. Biol. Chem., 270:44, 26037-26040.	
	ODA, S. et al (1992). Pharmacological profile of HS-142-1, a novel nonpeptide atrial natriuretic peptide (ANP) antagonist of microbial origin. II. Restoration by HS-142-1 of ANP-induced inhibition of aldosterone production in adrenal glomerulosa cells. J. Pharmacol. Exp. Ther., 263:1, 241-5.	
	O'DOWD, B.F., et al (1988). Site-directed mutagenesis of the cytoplasmic domains of the human BETA ₂ -adrenergic receptor. J. Biol. Chem., 263, 15985-15992.	
	PALKOWITZ, A.D. et al (1994). Structural evolution and pharmacology of a novel series of triacid angiotensin II receptor antagonists. J. Med. Chem., 37:26, 4508-21.	
	PARENT, J., et al (1996). Mutations of two adjacent amino acids generate inactive and constitutively active forms of the human platelet-activating factor receptor. J. Biol. Chem., 271:14, 7949-7955.	
	PARFITT, A.M., et al (1996). Hypercalcemia due to constitutive activity of the parathyroid hormone (PTH)/PTH-related peptide receptor: comparison with primary hyperparathyroidism. J. Clin. Endocr. Metab., 81, 3584-3588.	
	PARMA, J., et al (1993). Somatic mutations in the thyrotropin receptor gene cause hyperfunctioning thyroid adenomas. Nature, 365, 649-651.	
	PEI, G., et al (1994). A constitutive active mutant BETA ₂ -adrenergic receptor is constitutively desensitized and phosphorylated. Proc. Natl. Acad. Sci. (USA), 91, 2699-2702.	
	PENDLEY, C.E. et al (1993). The gastrin/cholecystokinin-B receptor antagonist L-365,260 reduces basal acid secretion and prevents gastrointestinal damage induced by aspirin, ethanol and cysteamine in the rat. J Pharmacol Exp Ther, 265:3, 1348-54.	
	PEROUTKA, S. (1995). Serotonin receptor subtypes. Their evolution and clinical relevance. CNS Drugs. 4, 19-28.	
	PETTIBONE, D.J. & CLINESCHMIDT, B.V. (1993). Development and pharmacological assessment of novel peptide and nonpeptide oxytocin antagonists. Regul Pept, 29, 45:1-2.	

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

	PRAT, M.P., et al (1991). The receptor encoded by the human C-MET oncogene is expressed in hepatocytes, epithelial cells and solid tumors. <i>Int. J. Cancer</i> , 49, 323-328.	
	PREZEAU, L., et al (1996). Changes in the carboxy-terminal domain of metabotropic glutamate receptor 1 by alternate splicing generate receptors with differing agonist-independent activity. <i>Mol. Pharmacol.</i> , 49, 422-429.	
	RAKOVSKA, A. et al (1993). Effect of loxiglumide (CR 1505) on CCK-induced contractions and 3H-acetylcholine release from guinea-pig gallbladder. <i>Neuropeptides</i> , 25:5, 271-6.	
	De Dios, I. & Manso, M.A. (1994). Effect of L-364,718 (CCK receptor antagonist) on exocrine pancreatic secretion of hydrocortisone-treated rats. <i>Pancreas</i> , 9:2, 212-8.	
	REN, Q., et al (1993). Constitutive active mutants of the ALPHA ₂ -adrenergic receptor. <i>J. Biol. Chem.</i> , 268, 16483-16487.	
	REYNOLDS, E.E. (1995). Pharmacological characterization of PD 156707, an orally active ETA receptor antagonist. <i>J. Pharmacol. Exp. Ther.</i> , 273:3, 1410-7.	
	ROBBINS, L.S., et al (1993). Pigmentation phenotypes of variant extension locus alleles result from point mutations that alter MSH receptor function. <i>Cell</i> , 72, 827-834.	
	RONG, S., et al (1993). Met expression and sarcoma tumorigenicity. <i>Cancer Res.</i> , 53:22, 5355-60.	
	SAMAMA, P., et al (1993a). A mutation-induced activation state of the B2-adrenergic receptor. <i>J. Biol. Chem.</i> , 268:7, 4625-36.	
	SAUTEL, M. et al (1996). Neuropeptide Y and the nonpeptide antagonist BIBP 3226 share an overlapping binding site at the human Y1 receptor. <i>Mol. Pharmacol.</i> , 50:2, 285-92.	
	SAWUTZ, D.G. et al (1995). Pharmacology and structure—activity relationships of the nonpeptide bradykinin receptor antagonist WIN 64338. <i>Can. J. Physiol. Pharmacol.</i> , 73:7, 805-11.	
	SCHEER, A. & COTECCHIA, S., (1997). Constitutively active G protein-coupled receptors: potential mechanisms of receptor activation. <i>J. Receptor & Signal Transduction Research</i> , 17(1-3), 57-73.	
	SCHEER, A., et al (1997). The activation process of the 1B-adrenergic receptor: potential role of protonation and hydrophobicity of a highly conserved aspartate. <i>Proc. Natl. Acad. Sci. (USA)</i> , 94, 808-813.	
	SCHWININ, D.A., et al (1995). Cloning and pharmacological characterization of human Alpha-1 adrenergic receptors: sequence corrections and direct comparison with other species homologues. <i>The J. Pharmacol.</i> , 272, 134-142.	
	SCHILD, L., et al (1995). A mutation in the epithelial sodium channel causing Liddle disease increases channel activity in the <i>Xenopus laevis</i> oocyte expression system. <i>Proc. Natl. Acad. Sci. (USA)</i> , 92, 5699-703.	
	SEEMAN, P. & VAN TOL, H. (1994). Dopamine receptor pharmacology. <i>Trends Pharmacol. Sci.</i> 15, 264-270.	

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

	SEEMAN, P. (1993). Dopamine D4 receptors elevated in schizophrenia. <i>Nature</i> , 365, 441-445.	
	SERRADEIL-LE GAL, C., et al (1993). Biochemical and pharmacological properties of SR 49059, a new, potent, nonpeptide antagonist of rat and human vasopressin V1a receptors. <i>J. Clin. Invest.</i> , 92:1, 224-31.	
	SHARIF, M., et al (1994). Malignant transformation by G protein-coupled hormone receptors. <i>Molecular & Cellular Endocrinology</i> , 100, 115-119.	
	SHOWERS, M.O., et al (1992). Activation of the erythropoietin receptor by the Friend spleen focus-forming virus gp55 glycoprotein induces constitutive protein tyrosine phosphorylation. <i>Blood</i> , 80, 3070-8.	
	SKINNER, R.H., et al (1994). Direct measurement of the binding of Ras to neurofibromin using scintillation proximity assay. <i>Anal. Biochem.</i> , 223, 259-265.	
	SLAMON, D.J., et al (1987). Human breast cancer: correlation of relapse and survival with amplification of the HER-2 neu oncogene. <i>Science</i> , 235, 177-182.	
	SLAMON, D.J., et al (1989). Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. <i>Science</i> , 244, 707-712.	
	SOLOMON, Y., et al (1974). A highly sensitive adenylate cyclase assay. <i>Anal. Biochem.</i> , 58, 541-548.	
	SPIEGEL, A.M., et al (1995). Defects in G protein-coupled signal transduction in human disease. <i>Ann. Rev. Physiol.</i> , 58, 143-170.	
	TER LACK, A., et al (1995). Modelling and mutation studies on the histamine H1-receptor agonist binding site reveal different binding modes for H1-agonists: Asp116 (TM3) has a constitutive role in receptor stimulation. <i>J. Computer-aided molecular design</i> , 9, 319-330.	
	TIBERI, M. & CARON, M.G. (1994). High agonist-independent activity is a distinguishing feature of the dopamine D1B receptor subtype. <i>The J. Biol. Chem.</i> 269:45. 27925-27931.	
	TSUJIMURA, T., et al (1996). Constitutive activation of c-kit in FMA3 murine mastocytoma cells caused by a deletion of seven amino acids at the juxtamembrane domain. <i>Blood</i> , 87, 273-283.	
	WANG, Z., et al (1994). Constitutive opioid receptor activation as a regulatory mechanism underlying narcotic tolerance and dependence. <i>Life Sciences</i> , 54:22, 339-350.	
	WATOWICH, S.S., et al (1992). Homodimerization and constitutive activation of the erythropoietin receptor. <i>Proc. Natl. Acad. Sci. (USA)</i> , 89, 2140-4.	
	WEBER-NORDT, R.M., et al (1996). Constitutive activation of STAT proteins in primary lymphoid and myeloid leukemia cells and in Epstein-Barr virus (EBV)-related lymphoma cell lines. <i>Blood</i> , 88:3, 809-16.	
	WEBSTER, K. & DONOGHUE, J. (1996). Constitutive activation of fibroblast growth factor receptor 3 by the transmembrane point mutation found in achondroplasia. <i>The EMBO J.</i> , 15, 520-527.	

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

		XU, Y.H., et al (1984). Characterization of epidermal growth factor receptor gene expression in malignant and normal human cell lines. Proc. Natl .Acad. Sci. (USA)., 81, 7308-7312.	
		YAMADA, K., et al (1992). Substitution of the insulin receptor transmembrane domain with the c-neu/erb2 transmembrane domain constitutively activates the insulin receptor tyrosine kinase in vitro. J. Biol. Chem., 267, 12452-12461.	
		ZHEN, Z., et al (1994). Structural and functional domains critical for constitutive activation of the HGF-receptor (<i>Met</i>).Oncogene, 9, 1691-1697.	

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

COPY